



PATENT
Customer No. 22,852
Attorney Docket No. 02481.1693

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of:)
HABERMANN et al.) Group Art Unit: 1653
Application No.: 09/664,326) Examiner: H. Schnizer
Filed: September 18, 2000)
For: SIGNAL SEQUENCES FOR)
PREPARING LEU-HIRUDIN BY)
SECRETION BY E. COLI INTO THE)
CULTURE MEDIUM)

MAIL STOP APPEAL BRIEF - PATENTS

Commissioner for Patents and Trademarks
P.O. Box 1450
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Sir:

REPLY BRIEF

Pursuant to 37 C.F.R. § 1.193, Appellants submit this Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer mailed January 26, 2004.

I. Status of the Rejections

In response to the Appeal Brief filed October 24, 2003, claims 6-9 remain rejected under 35 U.S.C. § 103(a) over Achstetter et al., 110 GENE 25-31 (1992), ("Achstetter") in view of EP 0 448 093 (for which U.S. Patent No. 5,919,895 is the English language counterpart) to Schmid et al. ("Schmid").

II. Response to Examiner's Answer

Appellants have considered the Examiner's Answer and, in view of it, have reviewed the references and the pending claims 6-9 again. Nevertheless, Appellants still do not observe, in either reference, any "clear and particular" evidence of a motivation to combine the references, as required by the case law. See *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999).

The Examiner alleges that "Appellants have not considered what the references teach as a whole." It is instead the Examiner who has failed to appreciate what both the references and the instant specification teach. The Examiner has mischaracterized the relevant state of the art by alleging that those of ordinary skill "knew of a construct that encoded a hirudin derivative fused to a signal peptide that could be expressed in an *E. coli* expression system . . ." Examiner's Answer at 7. To the contrary, Achstetter does not teach the use of *E. coli*, and Schmid does not use *E. coli*, but rather *E. coli* secretor **mutant strains**. The Examiner has not establish any teaching or suggestion in either Achstetter or Schmid that *E. coli* other than these specific secretor mutant strains can be used for the secretory expression of a desired hirudin or hirudin derivative protein.

In fact, as the Examiner herself admits, "[t]he bacteria, *E. coli*, [used in the Schmid patent] appears to be preferred because of the availability of *E. coli* strains which show massive protein secretion into the culture medium . . ." Examiner's Answer at 6. Yet, as Applicants clearly asserted in their Appeal Brief, the Applicants' claims are drawn to *E. coli*, and do not encompass the specific mutant strains of *E. coli* referenced in Schmid. This aspect of the invention would be clearly understood by one of ordinary skill in the art, interpreting the claims in light of the specification.

The Examiner states that “[l]imitations from the Specification are not read into the claims,” and the [p]resent claims do not exclude expression of *E. coli* secretion mutants.” Examiner’s Answer at 8. While Appellants note that the present claims are drawn simply to *E. coli*, when the claims are read in light of the specification, as claims must be, it is apparent to those of ordinary skill in the art that secretor mutants are not within the scope of the instant claims. *Markman v. Westview Instruments, Inc.*, 52 F.2d 967, 979 (Fed. Cir. 1995) (“Claims must be read in view of the specification, of which they are a part.”). When the specification “makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question.” *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.2d 1337, 1341 (Fed. Cir. 2001).

Notably, all of the examples compare the expression system of the invention with *E. coli* secretor mutants to illustrate the different yields obtained between the instant invention and secretor mutants. This positively excludes the presence of secretor mutants in the expression system of the invention.

The Examiner has misunderstood and is mischaracterizing the specification through her assertion that “all of the examples in the present Specification use the *E. coli* secretor mutant WCM 100 . . .” Examiner’s Answer at 8. This is not accurate. Rather, when the Examples are read carefully, one can see that the expression obtained through the process depicted in the Examples is only compared with the

expression obtained through the secretor mutant WCM 100, does not itself employ the secretor mutant:

Competent cells of the *E. coli* strain Mc1061, or the secretor mutant WCM 100, were transformed with the ligation mixture and grown under selection pressure on ampicillin-containing plates. The next morning, expression as described in Example 6 was then compared with Ala-hirudin expression using the *E. coli* strain WCM100/pCM7053. It was found that the expression obtained was about 1.5 times better than in the comparative test.

Specification at Example 1, page 9, ll. 1-6 (emphasis added). Likewise, Example 2 states that “[t]he expression was carried out by comparison with Ala-hirudin expression using the *E. coli* strain WCM100/pCM7053.” *Id.* at ll. 23-24 (emphasis added). Therefore, the Examiner’s assertion that the instant Examples use an *E. coli* secretor mutant is an unfortunate mischaracterization of Appellants’ Examples.

Furthermore, Appellants fail to see the relevance of the Examiner’s argument that Schmid does not explicitly state that the secretor mutants are essential to the increased expression obtained. According to the Examiner, “Schmid et al. implies that the sequences of the hirudin derivatives were more important for the high yields obtained [than the *E. coli* secretor mutants].” Examiner’s Answer at 9. Even assuming *arguendo* this statement is correct, this in no way would affect the non-obviousness of the present claims 6-9. Even if Schmid does in fact stress the hirudin derivative sequence rather than the *E. coli* used, than one of ordinary skill in the art would have less motivation, not more, to use *E. coli* “for selecting a signal peptide for secretory expression of a desired hirudin or hirudin derivative protein,” as claimed herein.

The Examiner additionally states that “Schmid et al. does not suggest that removal of the *E. coli* secretor mutants disclosed therein would have led to the previous

low levels of hirudin expression." Examiner's Answer at 11. Appellants disagree. Schmid clearly states that "in *E. coli* cells, the yield is relatively low and/or complicated isolation processes are necessary on disruption of the cells." Schmid, col. 2, ll. 17-19. Thus, Schmid clearly teaches that regular, non-mutated *E. coli* cells lead to a low yield of hirudin.

Therefore, as discussed in Appellants' Appeal Brief, one of ordinary skill in the art lacks not only the motivation or suggestion to combine Achstetter and Schmid, but likewise would lack any reasonable expectation of success from making this combination.

Accordingly, Appellants maintain their position on all issues covered by the Appeal Brief filed on October 24, 2004, and respectfully assert that a *prima facie* case of obviousness has not been established. Appellants respectfully request reversal of the rejections of claims 6-9 under 35 U.S.C. § 103(a).

III. Conclusion

To the extent any further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Reply Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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